



**Prequalification Team
WHO PUBLIC INSPECTION REPORT
Quality Control Laboratory**

Part 1: General information

Name of the QC Laboratory	State Scientific Research Laboratory on Quality Control of Medicines		
Physical address	State Institution “O.M. Marzeyev Institute for Public Health of the National academy of medical sciences of Ukraine” (SI “IPH NAMSU”), 50 Popudrenka str., Kyiv, 02660, Ukraine Web: www.druglab.kiev.ua		
Date of inspection	28, 29, 30 September 2015		
Type of inspection	Initial routine inspection		
Type(s) of testing included in the inspection	Chemical, physical, microbiological		
Summary of the testing activities performed by the QC Laboratory	<i>Type of analysis</i>	<i>Finished products</i>	<i>Active pharmaceutical ingredients</i>
	Physical/Chemical analysis	Clarity and degree of opalescence of liquids, degree of coloration of liquids, pH, density, osmolality, refractometry, optical rotation, viscosity, conductivity, water content, acid value, iodine value, peroxide value, ester value, hydroxyl value, saponification value, nitrogen determination, heavy metals, loss on drying, limit tests, disintegration, dissolution, uniformity of dosage units (mass, content), friability, tablet hardness,	pH, density, refractometry, optical rotation, viscosity, osmolality, conductivity, melting point, water content, acid value, iodine value, peroxide value, ester value, hydroxyl value, saponification value, unsaponifiable matter, nitrogen determination, heavy metals, loss on drying, limit tests



		dimensions, particulate contamination (sub-visible/visible particles)	
	Identification	HPLC (DAD, RID,UV-Vis, FLD), GC (FID, ECD), TLC, UV-Vis Spectrophotometry, FTIR spectroscopy, basic tests	HPLC (DAD, RID,UV-Vis, FLD), GC (FID, ECD), TLC, UV-Vis Spectrophotometry, FTIR spectroscopy, basic tests
	Assay, impurities and related substances	HPLC (DAD, RID,UV-Vis, FLD), GC (Au/HS(FID, ECD)), UV-Vis Spectrophotometry, FTIR spectroscopy, Water determination, basic tests	HPLC (DAD, RID,UV-Vis, FLD),GC (Au/HS(FID, ECD)), UV-Vis Spectrophotometry, FTIR spectroscopy, Water determination, basic tests
	Microbiological tests	Sterility test, microbial limit tests, bacterial endotoxins test (LAL), microbial assay of antibiotics	Sterility test, microbial limit tests, bacterial endotoxins test (LAL), microbial assay of antibiotics

Part 2: Summary

General information about the laboratory and site

The laboratory was in existence since 1986 for microbiological tests. Physico-chemical testing was initiated in 1996. It had 49 employees. They were accredited according to national law and to ISO 17025. The main activities were:

- quality control of medicines in the national monitoring system;
- testing the reproducibility of methods for quality control of drugs in the state system of drug registration;
- providing advice and guidance to businesses, organizations and institutions on the analysis of substances;
- testing products sampled by others from the market, as part of market monitoring;
- performance of testing for the Global Fund;
- contract testing for manufacturers who do not have the facilities to perform some of their own tests;



- participation in state proficiency testing (not yet in EDQM or WHO proficiency testing schemes).

History of WHO and/or regulatory agency inspections

This was the first WHO inspection. It had last been inspected on 15 May 2014 by the National Accreditation Agency of Ukraine as part of a supervisory audit for verification of conformance with State Standard of Ukraine ISO/IEC 17025:2006 “General requirements for the competence of testing and calibration laboratories”, in line with Accreditation certificate № 2H905 dated 28.05.2014.

Focus of the inspection

The inspection focussed on the quality management system and as the areas of quality control testing prequalified by the WHO.

Inspected Areas

The following areas of the WHO good practices for quality control laboratories were covered in this inspection:

- 2.1 Quality system
- 2.2 Control of documents
- 2.3 Records
- 2.4 Data-processing equipment
- 2.5 Personnel
- 2.6 Premises
- 2.7 Equipment, instruments and other devices
- 2.8 Reagents
- 2.9 Reference substances and reference materials
- 2.10 Calibration, verification of performance and qualification of equipment, instruments and other devices
- 2.11 Traceability
- 2.12 Incoming samples
- 2.13 Analytical sheet
- 2.14 Validation of analytical procedures
- 2.15 Testing
- 2.16 Evaluation of results
- 2.17 Certificate of analysis
- 2.18 Retained samples
- 2.19 Safety

(please note that the sections below have a different numbering than those of the WHO good practices for quality control laboratories.)



2.1. Organization and management

The Head of Quality, Internal Auditors and laboratory supervisors reported to her directly.

The Laboratory was part of the SI “O.M. Marzeyev Institute for Hygiene and Medical Ecology, NAMS of Ukraine” building. The premises of the Laboratory were located on three floors. Sample receipt and physico-chemical testing was performed on the 11th floor of the building. Microbiological testing took place on the 9th floor of the building.

2.2. Quality management system

Management review

The quality management system was verified during management review. Management review was done twice per year.

Each process was managed by a different person and the reports were submitted for each different division or process for management review. Management reviews considered several elements including the following:

- Questionnaires were sent to customers and the responses were evaluated;
- Internal audits;
- Proficiency testing, and inter analyst comparative testing results were consulted;
- Corrective and preventive actions (CAPA) and their effectiveness;
- Non conformities.

The management review from 1 July 2014 to 31 December 2014 was shown to inspectors. 61 questionnaires were sent to customers.

Each process had their own criteria for assessment during management review.

The register for complaints was also reviewed and had been started in 2007. There were no non-conformities.

Courses or seminars and the number of tests per analysts were documented as part of the analyst training requirements. There was an analysis of metrological and of calibration work done. Qualification of equipment located in the laboratory premises, such as fridges and deep-freezers was performed. There was some kind of point system used for evaluation of suppliers of the reagents and other materials. The laboratory did an analysis of the suppliers and reagents and analysis of the computer systems and software. CAPAs that were created further to this review were documented.

Corrective actions

The SOP entitled “Corrective action procedure” was reviewed. It was applicable to internal and external audits and to management requests for action, as well as to analyst errors, to environmental monitoring and to issues noted during the monthly evaluation of processes. Root cause has to be found in case if the person does something in non-conformance. The name of the person who has to do the corrective actions was specified. Date where they were implemented was also specified. Evaluation of the



effectiveness of the corrective actions was performed and a responsible person was assigned. Examples of corrective actions and preventive actions were selected and reviewed by inspectors.

Preventive actions

The SOP entitled “Preventive action procedure” was reviewed. Results of the inter-laboratory and proficiency testing were part of corrective actions and preventive actions (CAPA). The current register, opened in 2007, was reviewed. It included details such as the date of the recording and preventive actions, as well as the target. An explanation of the preventive actions was included.

Non-conforming test results

The SOP entitled “Procedure for out-of-specifications” was reviewed. It stated, in a flow chart, the process for checking the root cause, calculations, reference standards, equipment, reagents and environment in the laboratory, glassware, analyst error and finally, the sample. Once this is done, if they found out there were issues, they could repeat the test, if required. Repeat analysis was done by another analyst. They generally used the same product sample, but re-prepared new solutions. If the first analyst got an OOS and the 2nd one was passing, a third analysis was performed. If the third result was failing, the OOSs were then confirmed. An example was shown on a suspicious sample that was tested in 2014. The investigation report was available. Another example was shown regarding microbiology which was registered in a separate register for microbiology.

Internal audits

Internal audits were performed once per year process. Each process was audited separately and there were 11 processes, leading to a total of individual 11 audits. There were sub-processes under each process, such as gas chromatography (GC) and high performance liquid chromatography (HPLC) that were under the physico-chemical laboratory. A list of the auditors and certified internal auditors was available. An audit plan was established prior to the audit. Audit reports were drafted and finalized. Auditors performed the audit according to the check-list and the auditees provided them with the answers. Performance of the tests was monitored during the audits. If non conformities were found, a protocol of non-conformity was filled. Corrective and preventive actions were filled. The corrective actions were proposed by the auditee and verified. When the corrective and preventive actions were implemented, a final report was written, which was approved by the head of the laboratory. The report was written by the lead auditor.

2.3. Control of documentation

High level documents had a different format compared to actual SOPs.

2.4. Records

Records were a mixture of electronic (LIMS) and paper records. These were generally well maintained and acceptable in the most part.

2.5. Data-processing equipment

Calculations were performed using certain validated excel spreadsheets and by hand in the most part.



2.6. Personnel

Internal and external training was performed. At the beginning of the year, a training schedule was established. Practical verification follows the SOP entitled “Conducting of internal quality control of testing”. Practical verification was performed using known samples that were distributed to 4-5 analysts at a time. The head of the laboratory or the group lead monitors the performance of this test according to this list.

The most recent employee was hired in October 2011. The training period lasted 3 months, during which she was trained on the quality system, on safety, on methods of analysis. Tests were performed under monitoring by her supervisor. After this, there was a committee who verified the training record and thereby allowed the analyst to work individually. There were 4 people allowed to work with high performance liquid chromatography equipment (HPLC) and gas chromatography equipment (GC). Others were qualified to do all other tests. Individually, for each and every analyst, the kind of test that they were qualified to perform was documented.

Job descriptions were available for each employee and were signed off. Each employee’s qualification, resume and training, including certificates were stored in tracked in a LIMS database.

2.7. Premises

The premises were spacious and appropriately maintained in the most part.

2.8. Equipment, instruments and other devices

There were four analytical balances, ~~one~~ two HPLCs, two GCs, mass spectrometry, ~~two~~ one Karl Fisher, one polarimeter, one Fourier transform infrared spectroscopy (FTIR) and one ultra violet (UV)-visible.

2.9. Contracts

The contract with one of the service providers was reviewed.

The contract with the Central Laboratory for the Quality Control of Medicines was reviewed. It was considered acceptable.

2.10. Reagents

Procedure entitled “Receiving, storage and checking of expiry date of reagents” was reviewed. It stated that integrity of sealing, batch number and expiry date should be checked. It specified that the shelf-life should be specified to be within the certificate of analysis’s specified expiry date. Poisonous substances such as arsenic, or other inorganic compositions, barium salts and hydrazine, were stored along with the other liquid reagents. For poisons, the laboratory obtained permission from the ministry of Ukraine. There was no procedure stating the need for chemists to familiarize themselves with the MSDS.

There was a list of approved suppliers, to which they had sent a questionnaire. Scores were assigned based on the answers obtained from the suppliers (distributors/re-packagers).



2.11. Reference substances and reference materials

Standards were available. Expiry date was verified at the last day of each month. They disposed of expired standards but there were no records of the actual monthly removal of expired reference standards other than in the database. The expired standards were marked with the letter R in the database.

2.12. Calibration, verification of performance and qualification of equipment, instruments and other devices

Dissolution

There was one dissolution test equipment (multi-vessel). Performance verification was done in front of inspectors.

Balances

The balance qualification report for the balance XXX was verified. There were four different balances. Daily performance verification was done using 4 weights. Extended verification was done every three months.

2.13. Traceability

Logbooks and worksheets ensured traceability. Electronic data was also readily retrievable. Backed up data for HPLC was restored quickly upon demand, as demonstrated to inspectors.

2.14. Incoming samples

When samples arrived, they were taken to the 11th floor office, where they were registered in the LIMS system. If different products arrived with the same request, they were registered together. The number and date of the test request letter were entered along with the name of the requestor, batch numbers, procedures and type of test.

The sequence number and date were given. There were two persons working on the LIMS system, which was password protected. It records the outcome of the analyses for transmission to the test requestor.

The responsible person had access to all of the pharmacopoeias and the dossier electronically, which were in possession of the Ministry of Health. The latest version of the specifications filed with the dossier, were verified and available. The test sheet was prepared and sent to the analysts along with the samples. Samples were labelled with their unique sample number. A particular test request could be divided between two or three analysts. According to laboratory procedures, testing should be performed within 30 days from having received samples.

2.15. Analytical worksheet

Analytical worksheets were prepared prior to analysis. The analyst logbooks also served as analytical worksheets for recording raw data.

2.16. Validation of analytical procedures

Method validation or verification was not performed. Only system suitability should be done.



2.17. Testing

Dissolution

There were a sufficient number of syringes to withdraw samples obtained during dissolution.

HPLC

There were two HPLCs in use that were connected to computers. The main HPLC was equipped with a diode array detector. Another one that was used mostly for research purposes was equipped with a fluorescence detector.

Infrared spectroscopy

Analyses were recorded in the instrument logbook. Qualification and performance verification were performed according to a schedule and were up to date. During routine testing, sample spectra were compared to the reference standard spectra.

GC

All equipment was reported to be well functioning and with up to date qualification, calibration and maintenance.

Microbiology

Registers were kept for lyophilized strains and live strains which allowed to verify the number of passages. Morphological and biochemical identification was done. Incubators at temperatures of 23, 32 and 36 degrees, as noted by inspectors at the time of the inspection, were in use. Colonies were counted visually.

Prepared media was stored for up to one month. A laminar air glow booth was available. For reference strains, the first passage was used for one year, twelve passages were prepared at a time, after two passages per week (8 per month). Growth promotion was checked.

Sterility tests were carried out in laminar airflow cabinets (classified as grade A, surrounded by grade B).

Microbial enumeration was done in a grade B room. In this room, weighing of samples, sample preparation, samples pouring to the plates or to the flasks were performed.

Media was sterilized for 20 minutes at 121°C. The autoclave was purchased recently and was installed approximately one month before the inspection. Installation qualification, operational qualification and performance qualification were performed by the service provider and were documented. Small and large volumes were not sterilized together. Heat penetration tests were performed. This report was considered acceptable overall. Temperature and pressure was part of the printouts.

Environmental qualification was reviewed. It included reports for the laminar airflow and for the surrounding class B areas. The calibration certificates of the two particle counters that were used, was verified by inspectors and considered satisfactory.



2.18. Evaluation of test results

Tests were also performed using UV-visible spectrophotometry, a polarimeter, Karl-Fisher automatic titrimeter, dissolution tester, hardness tester, friability, preparative thin layer chromatography (TLC). Each test was recorded in the instrument's respective equipment logbook.

2.19. Certificate of analysis

Certificates of analysis were issued through data entry in LIMS. The contents of the certificate were double checked by the manager prior to her sign-off.

2.20. Retained samples

The laboratory retained samples for periods in accordance with local national regulations and had a large retained sample bank. All samples were tracked and registered in a LIMS database.

2.21. Safety

There were no eye wash showers or bottles. MSDS sheets were available only for specific chemicals.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken the, State Scientific Research Laboratory on Quality Control of Medicines, located at 50 Popudrenka str., Kyiv, 02660, Ukraine, was considered to be operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories for the scope activities listed below:

- Physical/Chemical analysis of finished pharmaceutical products and active pharmaceutical ingredients
- Microbiological analysis of finished pharmaceutical products and active pharmaceutical ingredients

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.